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ON

IODIPIN:

Its Physiological and Therapeutic Importance.

By LUDWIG HESSE.

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Though the recognised curative effects of Iodine have led to its very extensive therapeutic application, the disagreeable, and in some instances dangerous, action of this metalloid and its salts has given rise to a pressing demand for some Iodine compound that would be free from such objectionable properties, or have them only in a less degree. It would be unnecessary on this occasion to consider the relative merits and demerits of the Iodine preparations that are in most general use. My object is to direct attention to Iodipin—a preparation that has been but recently made known. Its preparation is based upon the well-known property of fat to combine with the halogen, the capability of forming Iodine addition compound being proportionate to the position of the fat in the series of unsaturated fat acids as their tri-glycerides. To effect the addition of Iodine in the preparation of Iodipin, sesame oil is treated with Iodine monochloride; other kinds of oil may be used for the purpose, but sesame oil is preferable on account of its great digestibility, freedom from taste, and general agreeable character to which attention has been directed by V. NORDEN and STÜVE.

Iodipin is prepared as an article of commerce by the firm of E. MERCK, at Darmstadt, in two states of concentration :

- 1.—10 per cent. Iodipin, containing 10 per cent. of the halogen, and applicable chiefly for internal administration.
- 2.—25 per cent. Iodipin, containing 25 per cent. of halogen, and specially adapted for injections.

The 10 per cent. preparation is scarcely distinguishable in appearance or taste from the natural sesame oil. When suitably kept it does not undergo decomposition, but preserves its character as a pale yellow oily liquid, having at 20° C. a specific gravity of 1.025, insoluble in water or alcohol, but readily soluble in either

benzene, chloroform or petroleum spirit. The ether solution shaken with silver oxide or mercuric oxide does not give off its iodine. When treated with caustic alkalies, iodipin is split up and the solution acidified with nitric acid gives a precipitate of argentic iodide on addition of a soluble silver salt. When Iodipin is mixed with fixed alkaline carbonates and incinerated, the aqueous solution of the ash gives the reactions of alkaline iodides. Mixed with concentrated sulphuric acid Iodipin becomes dark coloured and swells up. Above the dark coloured column of liquid there is a violet coloured zone of Iodine vapour. Iodipin does not dissolve in concentrated nitric acid, but when heated with it to the boiling point becomes dark coloured and suddenly evolves Iodine vapour with explosive force.

The 25 per cent. preparation has the appearance of a thick viscous oily liquid of the consistence of honey in cold weather, and then requiring to be warmed before it is fit for use. It has a specific gravity of 1.227, and gives all the reactions above described in the case of the 10 per cent. Iodipin. It is more or less red or violet coloured, but the colour is not the result of decomposition, and is attributable in some way to the sesame oil, which is stated by MERKLING to contain a minute quantity of a resinoid substance; by VILLAVEECHIA and FABRIS an alcoholic oil which gives with several re-agents the well-known Boudouin reaction that is observed in greater or less degree with the high percentage Iodipin.

The careful physiological observations, instituted principally by WINTERNITZ, show that the absorption of Iodipin takes place not in the stomach, but almost invariably in the intestine. They also prove that the Iodized fat introduced into the system is for the most part deposited as such, and does pass into the circulation. If Iodipin were subject to rapid oxidation in the system the Iodine thus set free in considerable amount might be productive of deleterious effects; but in regard to the doses employed for medicinal purposes that possibility need not be considered. The deposition of Iodipin in the body holds good, not only in regard to that administered *per os*, but also for that administered subcutaneously, as well as *per rectum*. The investigations relating to rectal absorption are not, however, yet complete.

The assimilation of Iodized fat takes place generally. Not only does the rendered fat of the abdominal cavity and the subcutaneous cellular tissues contain Iodine, but Iodine is also

present in the ether extract of almost all the organs, especially the muscles and the bones. Next to the liver the bone marrow contains the largest amount of Iodine.

The Iodized fat does not pass into parts of the body with its original amount of Iodine, a small proportion of that amount being previously separated. According to WINTERNITZ that takes place through the minutely divided fat globules circulating in the blood being altered superficially by contact with alkaline salts, while the interior portions of the fat globules retain the full amount of Iodine.

The circumstance that the assimilated Iodized fat is partially deposited in the interior of the body, and that, consequently, considerable quantities of Iodine may be introduced by means of Iodipin without danger, constitutes a very advantageous distinction between that preparation and certain other new Iodine media.

The investigations carried out by SCHEELÉ have demonstrated that the consumption of Iodovasogen is not to be regarded as constituting a substitute for internal administration of potassium iodide, and WINTERNITZ has also shown that the consumption of Iodine in the form of vaselinol, Iodovasogen or potassium iodide, together with simultaneous consumption of food containing fat or fat forming ingredients, does not have the effect of causing any appreciable assimilation of Iodine in the body. Assimilation takes place under such conditions only when potassium iodide is administered, and only to a minute extent at three places—in the bone marrow, in the lacteal glands and in the hair. These observations have been fully confirmed by BENEDIX and CASPARI. The latter proved that when a solution containing potassium iodide and free Iodine was administered under the most favourable conditions there was no recognizable synthesis of iodized fat ; on the other hand he proved that when iodized fat was consumed no inconsiderable quantity of it passed from the food into the milk.

On the basis of such observations there is reason for regarding Iodipin from a physiological point of view as a highly interesting preparation, the advantage of which centres in the fact that it is partially assimilable in the body and then is capable of gradually supplying from that store of iodine sufficient quantities in proportion to the progress of oxidation, and the action exercised by the alkalinity of the blood to develop its effects.

Granting that an hereditary or acquired predisposition or a similar condition produced by sickness may be one of the chief determining causes of the accessory effects of Iodine, it must also be remembered that for accessory effects to be produced, the occurrence of assimilation or excretion is essential, and that acute iodism depends upon the irritating action of Iodine or Alkaline iodides upon the alimentary canal. In the case of Iodipin the conditions of assimilation and elimination are essentially different from those obtaining in regard to alkaline iodides and other Iodine preparations. With the former a few minutes are sufficient to allow of the salt being diffused in considerable quantity from the stomach in the secretions and excreta.

When Iodipin is administered *per os* Iodine appears in the urine within ten or fifteen minutes; but the elimination of the entire quantity taken does not take place within a short space of time, but, in contradistinction to the results produced by other Iodine preparations, only after a much longer period has elapsed. The elimination of Iodine is still more retarded when Iodipin is administered subcutaneously. KLINGMÜLLER and LOWENHEIM found in experiments with animals, that even after the lapse of seventy days there were still traces of Iodine in the urine. When Iodipin is assimilated as a result of subcutaneous injection it is turned to account in the most effective manner. KLINGMÜLLER was unable in repeated trials to obtain any evidence of Iodine in the fœces in a state of organic or inorganic combination.

In the administration of Iodipin therefore, Iodine is not only more gradually and uniformly eliminated than when administered in any other state of combination, and the diseased organism is consequently subjected to its influence more continuously and equally; but it may also be expected that the iodized fat is assimilated at the seat of disease and is there gradually liberated to exercise its heating influence. There is therefore no necessity to consider the questions whether the Iodine deposited with iodized fat is deposited as such and is there transformed in the circulation into alkaline iodide or whether the assimilatory properties of the Iodine salts thus formed in the system are to be ascribed to the influence exercised by leucocytes in such a manner that the alkaline iodide present in the blood or in the tissues is decomposed at the seats of greatest metamorphosis, that is to say, in the leucocytes, and thus liberated Iodine endowed with even increased assimilatory capacity.

Besides the elimination of Iodine as potassium iodide through the kidneys, some is also eliminated through the salivary glands. According to KLINGMÜLLER, there is also in addition to the conversion of Iodine into potassium iodide, another form of conversion in the organism which manifests itself in the excretion of an organic Iodine compound in the urine. At present the question whether this kind of Iodine metamorphosis is of the therapeutic importance has not yet been settled.

All observers are in accord that the use of Iodipin as anticipated is not attended with those disagreeable accessory effects that are so marked a result of the administration of potassium iodide. When administered internally, Iodipin very rarely causes iodism, and when it does occur, the symptoms are not so pronounced or extended as in the case with the alkaline iodides.

On the contrary, favorable mention is made of the influence exercised by Iodipin on the alvine evacuation and the increase of nutrition brought about as a consequence of internal or subcutaneous administration of Iodipin. Similar evidence is given as to the absence of any disinclination to taking it. In the case of some patients who are sensitive to the oily taste, it has been administered with warm milk or coffee, or mixed with some peppermint oil or cognac, and after each dose it is advisable to chew a piece of brown bread.

Naturally it might be anticipated that Iodipin would prove useful in all diseases in the treatment of which iodine salts has been found beneficial. These expectations have been fully confirmed. O. FRESE has employed it in cases of bronchitis, bronchial asthma and emphysema with very satisfactory results, and he has administered the 10 per cent. preparation in doses of two or three tea-spoonfuls daily. FRESE's experience was thoroughly confirmed by KINDLER, who found that asthmatic patients treated with Iodipin very rapidly obtained relief of bronchial symptoms. The chief applications of Iodipin are in the treatment of the manifold forms of scrophulous and syphilitic disorders. Reports as to its use in such cases are published by LOSIO, BURKHART, ROSENTHAL, RADESTOCK, and more especially KLINGMÜLLER. All observers agree as to the efficiency of the preparation. In the treatment of all kinds of tertiary syphilis the use of Iodipin is stated to give especially good results, whether the symptoms of disease present themselves in the muscles, the bones, the intestines, or

the nervous system. Similar results are reported in cases of arterial or other forms of vascular aneurism, as well as in some cases of tabes.

BURKHART prescribes Iodipin in daily doses of two or three tea-spoonfuls. RADESTOCK, who holds that all Iodine preparations should be administered in much larger doses than have hitherto been customary, prescribes Iodipin in doses of 40 to 50 grammes daily. For administration in such large doses no preparation could be more suitable than Iodipin on account of its being uniformly and gradually assimilated. KLINGMÜLLER carried out a very large number of observations in the Neisser Hospital at Breslau, and he decidedly prefers to administer Iodipin subcutaneously (not intra-muscular) rather than *per os*. Among several hundred cases in which it was injected, he has never met with one instance of Iodism being caused, as was incontestibly shown by the fact that the subcutaneous injection was not accompanied by any disturbance of the stomach or intestines. Moreover, Iodipin is absolutely non-toxic, even when administered subcutaneously in very large doses, and in the case of patients who cannot or will not take Iodipin *per os*, it is possible by means of subcutaneous administration to carry out a vigorous treatment with Iodine; that the Iodine administered in that manner is assimilated and actually becomes efficacious has already been shown. The elimination of Iodine after injection takes place somewhat slowly, not until after the lapse of from two to five days. It is therefore desirable at the outset to accompany the injection method with internal administration if it be requisite to produce an effect rapidly. Subcutaneous injections can be carried out in the gluteal region or in the skin of the back; they do not cause pain or inconvenience. For this purpose the 25 per cent. preparation is to be preferred, because of the smaller quantity necessary for introducing a given dose of Iodine. KLINGMÜLLER declares that Iodipin has a quite specific action in cases of tertiary syphilis. Both KLINGMÜLLER and KINDLER consider that subcutaneous injection is the most convenient and appropriate method of administering Iodipin. Both agree that the injection of large doses is free from danger, and that curative results are most rapidly effected in that way. They inject 10c. cm. of the 25 per cent. preparation daily in the gluteal region and for several days in succession. Before being used the preparation requires to be warmed to the temperature of the body, and the canulæ used should be as wide as possible, pushing them gradually under the

skin after having rendered the spot anæsthetic by the application of ethylchloride. The injection is painless and does not lead to the formation of abscess.

Reports of the satisfactory effects of Iodipin in cases of habitual headache, adipositas nimia, scrofulous affections of the ear, neck and eyelids have been made by many observers. Even in the worst cases of long standing tertiary syphilis, accompanied by destructive change of the muscular tissues and bones, the beneficial action of Iodipin has not been found to fail. The persistent pain in the limbs and bones has been relieved, the general sensation and the appearance of the patients being also improved. Similar results have attended the use of Iodipin in numerous cases of primary and secondary, as well as hereditary syphilis. KINDLER's experience was of the same nature. Syphilitic patients with bad brain symptoms, who had been treated without effect with potassium iodide showed improvement within five days after the commencement of injection of Iodipin. In the case of one patient suffering from spinal syphilis with pains in the back, spasms of the right leg and incontinence of urine, very excellent results were produced. The incontinence first subsided then the spasms and the pains of the back without any bad effects being apparent in any of the cases. Similar results were obtained with a patient suffering from syphilitic abscess and ulcerations of the nose, who had undergone various forms of treatment by inunction. After six days' treatment with Iodipin the abscesses healed.

Quite recently Iodipin has been made the subject of physiological investigation. Proceeding from the fact established by WINTERNITZ, that under normal action of the stomach the saliva gives indications of containing Iodine within a quarter of an hour to three-quarters of an hour after Iodipin has been administered, WINKLER and STEIN have made use of this means to ascertain disturbances of the functions of the stomach. They made use of freshly prepared starch paste paper, saturated in a dark place with a 5 per cent. solution of ammonium persulphate. Strips of this paper were moistened at one end with saliva every fifteen minutes. The smallest trace of Iodine was rendered perceptible by the coloration of the paper until its intensity increased to dark blue. The occurrence of this reaction was, however, very much retarded when the function of the stomach was disordered as in gastropotosis, dilatation of the stomach, and carcinoma

Although Iodipin has only been recently introduced, this addition to the resources of medicine has already gained many friends, and the results of experience gained with it afford reason for believing that in Iodipin a very valuable remedy has been placed at the disposal of the practitioner that will continue to command attention.

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DIRECTIONS FOR SUBCUTANEOUS INJECTION OF IODIPIN.—DR. NEISSER'S KGL. UNIV.-KLINIK FOR DISEASES OF THE SKIN AT Breslau.—Iodipin containing 25 % of iodine is injected into the gluteal region to the extent of 20C cm daily for ten successive days. The preparation should be previously warmed to the body temperature. This average dose of 20C cm may be varied as occasion requires. A syringe with wide discharge aperture, and a wide canula should be used because the preparation is difficult to inject on account of its thick syrupy consistence. For convenience of handling the syringe should have a transverse arm. The canula should be from 5 to 7 cm long, so as to be inserted obliquely under the skin as far as possible, and then the puncture closes better after the canula is withdrawn, and a piece of adherent plaster should be applied to prevent the Iodipin oozing out. Intermuscular injections are to be avoided as they give rise to a sense of tension and much pain. To avoid danger of injecting into a vein it is advisable after making the puncture to remove the syringe from the canula and wait to see whether blood flows.

